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3-Dimensional Bifurcation Angle Analysis in Patients With Left Main Disease

A Substudy of the SYNTAX Trial (SYNergy Between Percutaneous Coronary Intervention With TAXus and Cardiac Surgery)

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Objectives We explore the bifurcation angle (BA) parameters of the left main coronary artery (LM), the effect of percutaneous coronary intervention (PCI) on this angulation, and the impact of BA on clinical outcome.

Background The BA is emerging as a predictor of outcome after PCI of bifurcation lesions. Three-dimensional (3D) quantitative coronary angiography (QCA) overcomes the shortcomings of 2-dimensional analysis and provides reliable data.

Methods This is a substudy of the SYNTAX (SYNergy Between Percutaneous Coronary Intervention With TAXus and Cardiac Surgery) trial. The cineangiograms of the 354 patients who underwent PCI of their LM stem were analyzed with 3D QCA software (CardiOp-B, Paieon Medical, Ltd., Rosh Ha'ayin, Israel). The proximal BA (between LM and left circumflex [LCX]) and the distal BA (between left anterior descending and LCX) were computed in end-diastole and end-systole, both before and after PCI. The cumulative major adverse cardiac and cardiovascular event (MACCE) rates throughout the 12-month period after randomization were stratified across pre-PCI distal BA values and compared accordingly.

Results Complete analysis was feasible in 266 (75.1%) patients. Proximal and distal BA had mean pre-PCI end-diastolic values of 105.9 ± 21.7° and 95.6 ± 23.6°, respectively, and were inversely correlated ($r = -0.75$, $p < 0.001$). During systolic motion of the heart there was an enlargement of the proximal angle and a reduction of the distal angle (ΔBA −8.2° and 8.5°, respectively, $p < 0.001$ for both). The PCI resulted in a mean decrease in the distal BA (ΔBA 4.5°, $p < 0.001$). The MACCE rates did not differ across distal BA values; freedom from MACCE at 12 months was 82.8%, 85.4%, and 81.1% ($p = 0.74$) for diastolic values (first through third tertile).

Conclusions Left main BA analysis with 3D QCA is feasible. Both proximal and distal angles are affected by cardiac motion; PCI modifies the distal angle. There is no clear difference in event rates across pre-PCI distal BA values. (J Am Coll Cardiol Intv 2010;3:41–8) © 2010 by the American College of Cardiology Foundation

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The optimal treatment of left main coronary artery (LM) disease remains contentious (1,2), with much of the debate focused on the treatment of its distal part (3,4). Despite increasing data on LM interventions (5–8), the importance of anatomical parameters such as the bifurcation angle (BA) has not been fully appreciated (9).

A number of clinical (10–13) and bench (14,15) studies identify the significance of this angle in predicting the immediate procedural success or the long-term outcome. Limitations to previous studies include ambiguity in the definition of the BA and the specific stenting techniques. The most prominent limitation is that almost all relevant clinical studies rely on 2-dimensional (2D) analysis. The LM bifurcation is particularly difficult to image, because of foreshortening and vessel overlap (16); 3-dimensional (3D) quantitative coronary angiography (QCA) overcomes these shortcomings of 2D analysis and might be beneficial in this setting (16–18).

Abbreviations and Acronyms

BA = bifurcation angle
LAD = left anterior descending coronary artery
LCX = left circumflex coronary artery
LM = left main coronary artery
MACCE = major adverse cardiac and cardiovascular events
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
SB = side branch
TLR = target lesion revascularization
3D = 3-dimensional

The purpose of this study was to test the feasibility of assessment of the LM BA with a 3D QCA algorithm, describe the angulation parameters before and after PCI and evaluate their impact on the clinical outcome of the patients.

Methods

Study population. This is a substudy of the SYNTAX (SYNergy Between Percutaneous Coronary Intervention With TAXus and Cardiac Surgery) trial (19), which was a prospective, randomized, all-comers clinical trial with the overall goal of assessing the optimum revascularization treatment for patients with *de novo* 3-vessel disease or LM disease (either isolated or in combination with 1-, 2-, or 3-vessel disease). Patients (n = 1,800) suitable for either treatment option were randomized to PCI with polymer-based, paclitaxel-eluting TAXUS Express (Boston Scientific Corp., Natick, Massachusetts) stents or coronary artery bypass graft surgery; they were also stratified according to the presence or absence of LM disease. For the purpose of this study, we reviewed the cineangiograms of the 354 patients who underwent PCI of the LM stem. Patients with both bifurcation and nonbifurcation LM lesions were included in the study population.

This study was performed in Cardialysis BV (Rotterdam, the Netherlands) as an exploratory analysis and was not subsidized by the official sponsor of the trial, Boston Scientific Corporation. Prior permission was sought and granted by the Steering Committee to access and analyze this dataset.

Analysis method. Three-dimensional reconstruction was performed offline by 2 experienced operators (C.G. and Y.O.), blinded to individual patient data and clinical outcome, with a validated (20) program for 3D QCA (CardiOp-B system version 2.1.0.151, Paieon Medical, Ltd., Rosh Ha'ayin, Israel); the sequence of a single 3D reconstruction has already been amply described elsewhere (21–23). The software algorithm rendered an image as well as quantitative information including BA values; these were derived from images without any guidewires in place, which could modify the angle.

Two angles are presented in accordance with the European Bifurcation Club consensus document (9). Proximal Angle A is defined as the angle between the proximal main vessel and the side branch (SB), whereas distal Angle B is delineated between the distal main vessel and the SB (Fig. 1). By convention the left anterior descending coronary artery (LAD) was designated as the distal main vessel, and the left circumflex (LCX) as the SB. The LM bifurcation was designated as Y-shaped for distal BA values $<70^{\circ}$.

Study design. Three-dimensional reconstructions were performed before and after PCI. To assess the effect of the systolic-diastolic motion on the LM bifurcation angulation, separate 3D images were reconstructed for the end-diastolic and -systolic frames, both before and after the procedure. Systolic-diastolic variation of BA equals the difference of the respective end-diastolic and -systolic values.

Analysis was deemed complete, only if all 4 of the 3D images that were required were successfully reconstructed; outcome of each individual case study was categorized as partially analyzable or nonanalyzable, in cases where <4 or no images at all, respectively, were obtained.

The primary clinical end point of the trial was a composite of major adverse cardiac and cardiovascular events (MACCE) (death from any cause, stroke, myocardial infarction, or repeat revascularization) throughout the 12-month period after randomization.

Statistical analysis. Statistical analysis was performed with SPSS version 16.0 for Windows (SPSS, Inc., Chicago, Illinois) and SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina). Continuous variables are expressed as mean $\pm$ 1 SD and compared between groups by unpaired Student *t* test; paired *t* test was employed for within-group comparisons. Categorical variables are expressed as counts and/or percentages. Correlations between continuous variables were performed with the Pearson coefficient. Cumulative survival free of adverse events was calculated according to the Kaplan-Meier method and compared across the median and the tertile values of pre-PCI distal BA with the log-rank test. All statistical tests were 2-sided, and a p value <0.05 was considered statistically significant.

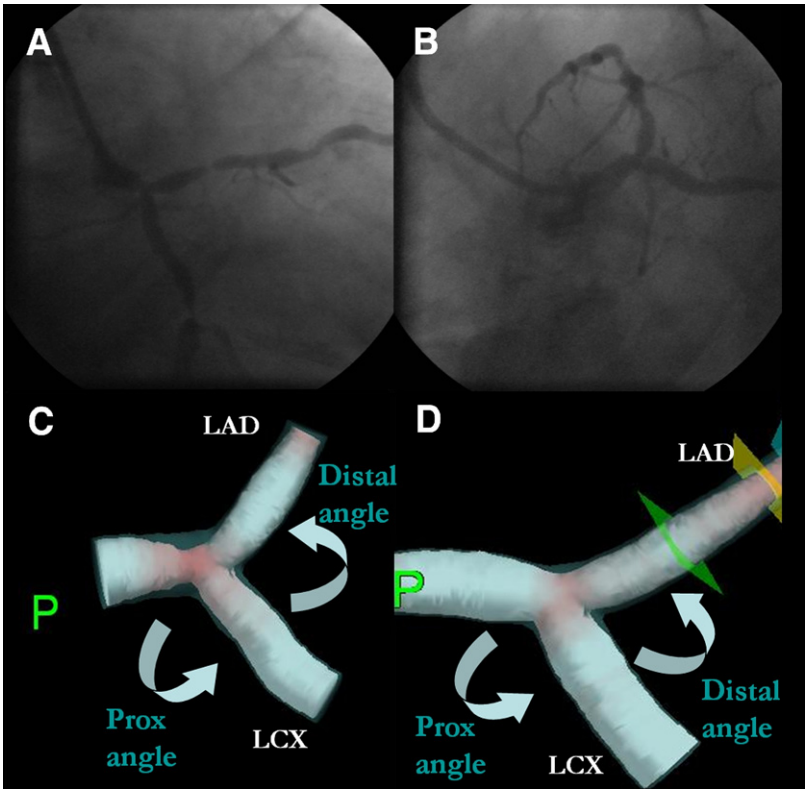

Figure 1. 3D BA Analysis

Two 2-dimensional single-plane angiographic images displaying the left main coronary artery (LM) bifurcation, one filmed in a right anterior oblique caudal view **(A)** and one in a left anterior oblique caudal view **(B)**, are post-processed; the 3-dimensional (3D) reconstructed image **(C)** is created. The proximal angle is defined between the LM stem and the left circumflex (LCX); the distal angle is defined between the left anterior descending (LAD) and LCX. After percutaneous coronary intervention **(D)** the proximal bifurcation angle (BA) is enlarged, whereas the distal BA gets narrower (CardiOp-B, Paieon Medical, Ltd., Rosh Ha'ayin, Israel).

Results

Complete 3D QCA analysis was feasible in 266 (75.1%) patients. The baseline demographic data and clinical characteristics of these patients are reported in Table 1. Total SYNTAX score (24) measured 29.9 ± 13.2. Stents were placed across the LM bifurcation in 185 cases; 1 stent was used in 75 cases, whereas ≥2 stents were used in 110 cases. Only 8.8% of all patients had isolated LM disease without additional diseased vessels.

Feasibility of analysis with 3D QCA. Beyond the 266 cases completely analyzed, another 88 could be analyzed either partly or not at all (48 and 40 cases, respectively). Less than complete analysis was attributable to 3 main reasons: 1) inadequate cineangiography and difficult anatomy in 42 cases; these cases displayed overlap and/or tortuosity of the branch vessels, particularly in their proximal segments; appropriate demarcation of the bifurcation was also compromised by a very short LM stem or a very small LCX (<1.5 mm); 2) failure to record 2 separate angiographic projections in 23 cases; in most of them, the final result of the procedure was filmed in a single projection, usually the operator's working view; and 3) 23 studies could not be processed with the 3D QCA software, mostly due to digitization in a non-DICOM (Digital Imaging and Communications in Medicine) format.

Baseline descriptives of LM BA. In the completely analyzable cohort (n = 266), distal and proximal BA had mean pre-PCI end-diastolic values of 95.6° ± 23.6° and 105.9° ± 21.7°, respectively. Distal and proximal BA values were inversely correlated ($r = -0.75$, $p < 0.001$), followed a normal distribution, and ranged from 44° to 165° and from 54° to 168°, respectively.

Effects of cardiac motion. End-systolic mean values of distal and proximal BA were 87.1° ± 22.9° and 114.0° ± 19.6°, respectively; there was a statistically significant effect of systolic motion on both parameters, a mean decrease of 8.5° ($p < 0.001$) for the distal BA, and a mean increase of 8.2° ($p < 0.001$) for the proximal BA. A similar effect was seen with post-procedural values, at the same level of statistical significance.

Table 1. Patient Demographic Data and Clinical Characteristics (n = 266)

Age (yrs)	65.2 ± 9.8
Male	73.7
BMI (kg/m^2)	28.2 ± 5.0
Diabetes mellitus	23.7
Insulin-requiring	6.0
Noninsulin-requiring	17.7
Hypertension	68.6*
Hyperlipidemia	80.5
Current smoker	20.3
Prior myocardial infarction	27.2
Unstable angina	29.7
Revascularization priority	
Emergent	3.0
Urgent	7.1
Elective	89.9
Additive EuroSCORE	3.8 ± 2.8
Total Parsonnet score	8.7 ± 7.6

Values are mean ± SD or %. *Data available in 264 patients.
BMI = body mass index; equals weight in kilograms divided by the square of the height in meters.

Effects of PCI on angulation. The effects of PCI on BA are summarized in Table 2. A PCI conferred a significant mean decrease in the distal BA (ΔBA = 4.5°, p < 0.001) (Fig. 2), whereas the proximal BA increased by a mean of 2.0° (p = 0.064). However, studying the Y-shaped LM bifurcations (13.9%) separately, the opposite phenomenon was apparent; distal BA increased after PCI by a mean of 10.3° (p = 0.001) and proximal BA decreased by 5.5° (p = 0.056). There was substantial individual variation for each angiographic study. PCI had equivalent impact on the end-systolic BA values.

Impact of BA on outcome. Outcome data to 12 months stratified and compared across pre-PCI distal BA tertiles is reported in Table 3. Freedom from MACCE was not significantly different whether diastolic or systolic values were analyzed; respective tertiles were <82°, 82° to 106°, and >107° and <77°, 77° to 96°, and >97°. Analysis with the median values (96° and 86°, respectively) as cutoff had a similar result.

Similar analysis of the subgroups where 1 stent or ≥2 stents were used in the LM bifurcation did not produce any significant differences between tertiles either (Fig. 3).

Discussion

The main findings of this study are: 1) 3D BA analysis seems feasible, even in this demanding angiographic setting; 2) there is a large variation in the angulation parameters of the LM; 3) cardiac motion modifies the bifurcation angulation; systolic motion results in a reduction of the distal and an enlargement of the proximal BA; 4) PCI treatment modifies the distal BA; overall, angles get narrower after PCI, whereas Y-shaped LM bifurcations increase their distal BA after the procedure; and 5) MACCE rates throughout 12 months after randomization did not differ across pre-PCI distal BA values.

The European Bifurcation Club has consistently been advocating the importance of BA measurements for the prediction of procedural outcome (9,25). The unique nature of the LM bifurcation requires the greatest possible accuracy in measurements, provided by 3D QCA algorithms (16–18).

Feasibility and advantages of 3D analysis. Inadequate cineangiography and difficult anatomy were the main reasons for less than optimal analysis in our study. Vessel overlap and foreshortening are well-known pitfalls of 2D analysis; resorting to operator expertise is not always the answer for acquiring the optimal projections (26). In the last 10 years evidence has accumulated that 3D angiographic reconstruction is accurate, sensitive, and reproducible (17,18,20,27–30) with a high degree of correlation for BA measurements in phantom studies (18). Reduced time requirements for a single 3D reconstruction (<60 s) with real-time analysis facilitate the choice of optimal gantry positions. Thus, we believe that, in a prospective study where operators are obtaining cineangiograms with the view to perform this kind of analysis, the number of non-analyzable cases could be limited to <10%.

Baseline angulation parameters of the LM. Upon review of relevant published reports, there is a single 2D-based angiographic study by Chen et al. (12) reporting on the BA in 37 LM patients submitted to crush stenting; distal BA had a mean value of 76° ± 24° and came up as an independent predictor of target lesion revascularization (TLR).

Three recent multislice computer tomography studies provide more than conventional angiographic data. Kawasaki et al. (31) studied the angles of the LM bifurcation in 209 patients and calculated a mean value of 72° for the distal LM angle. Pflederer et al. (32) reported an average value of 80° ± 27° for the angle between LAD and LCX, and Rodriguez-Granillo et al. (33) reported a median distal LM BA of 88.5° with an interquartile range of 68.8° to

Table 2. Pre- Versus Post-PCI Angulation Parameters (n = 266)

	Pre-PCI	Post-PCI	p Value*
Diastolic proximal BA, °	105.9 ± 21.7	107.9 ± 21.4	0.064
Systolic proximal BA, °	114.0 ± 19.6	114.5 ± 18.6	0.621
SDV-proximal BA, °	8.2 ± 13.2	6.7 ± 12.3	0.118
Diastolic distal BA, °	95.6 ± 23.6	91.1 ± 22.0	<0.001
Systolic distal BA, °	87.1 ± 22.9	83.0 ± 20.8	<0.001
SDV-distal BA, °	8.5 ± 12.5	8.1 ± 12.7	0.670

*Paired *t* test, 2-sided, p significant <0.05.
BA = bifurcation angle; PCI = Percutaneous coronary intervention, SDV = systolic-diastolic variation.

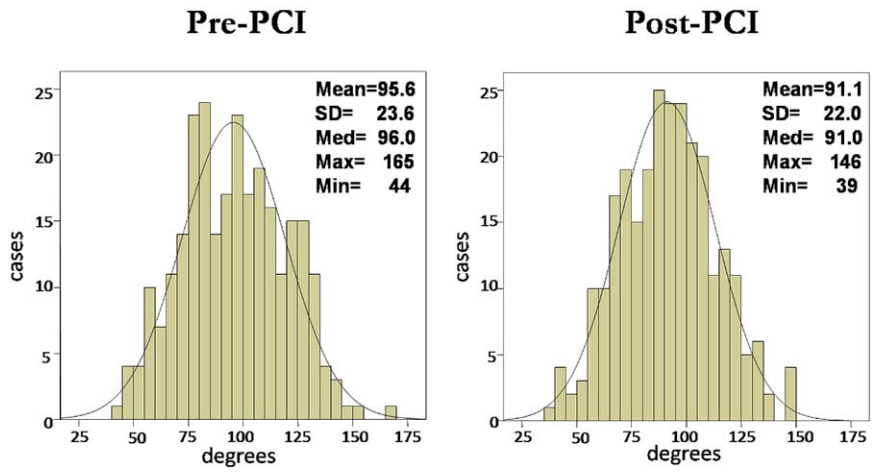

Figure 2. BA Values Distribution

Histograms of end-diastolic distal bifurcation angle (BA) values before and after percutaneous coronary intervention (PCI) with superimposed normal curves; values are in degrees. Post-PCI mean values are significantly decreased ($p < 0.001$). Descriptive statistics (mean ± SD, median, maximum, and minimum) are provided as well.

101.4°. An important finding of this study was that the more diseased individual vessels were, the wider the BA was.

Our study was based on 354 patients submitted to PCI of the LM stem; notwithstanding the increased mean distal BA values, the variation of our findings is comparable to previous studies. As a matter of fact, Kawasaki measured the angle complementary to the proximal BA, which is by definition narrower than the angle between the 3D reconstructed centerlines of the distal vessels, the one measured in our study.

Systolic-diastolic variation of BA values. The enlargement of the proximal BA and the reduction of the distal BA during systolic motion of the heart is a novel finding unaccounted for in the published data, possibly because deemed trivial or obvious. However, we feel that, from a methodological point of view, authors should define what BA values they are reporting on, because of their significant systolic-diastolic variation.

Table 3. Freedom From MACCE Across Pre-PCI Distal BA Tertiles (n = 266)

	1st Tertile	2nd Tertile	3rd Tertile	p Value*
Diastolic BA				
30 days	95.4%	95.5%	94.4%	
6 months	90.8%	89.9%	86.7%	
12 months	82.8%	85.4%	81.1%	0.74
Systolic BA				
30 days	95.4%	96.6%	93.4%	
6 months	89.7%	89.8%	87.9%	
12 months	80.5%	84.1%	84.6%	0.77

*Log-rank test between groups, p significant <0.05.
BA = bifurcation angle; MACCE = major adverse cardiac and cardiovascular events; PCI = percutaneous coronary intervention.

Impact of PCI on the angulation. Louvard et al. (34) reported that even the temporary insertion of an angioplasty guidewire is sufficient for the BA to be considerably modified. This leads us to believe that the permanent implantation of 1 or even 2 rigid metallic structures across the bifurcation would modify the angulation.

Another debatable issue is the extent and the direction of modification of the angulation parameters. As evidenced by our data, the distal BA is the primary variable modified. It seems that, overall, angles are decreased, whereas the narrowest pre-PCI angles are increased. Dvir et al. (35), with CardiOp-B software, have recently reported on the impact of PCI on the distal BA in 27 patients. Apart from provisional stenting, where the angle was not modified, every other technique or anatomy has resulted in a decrease in distal BA. Di Mario et al. (36) has also reported on single and double stent techniques and the change conferred, if any, on the BA. This was a subgroup analysis of the TRUE (TAXUS in real life usage evaluation) registry, comprising 1,069 patients and 191 bifurcations. Double stent techniques, particularly Culotte and Crush, significantly decreased the distal BA, whereas implantation of a single stent induced a nonsignificant increase. In a similar report from Kaplan et al. (37), distal BA was actually increased after T stenting yet by a modest 2°; in regard to Culotte, previous findings were reproduced.

Impact of BA on outcome. The impact of BA on immediate procedural success or long-term outcome is discussed in many studies. Dzavik et al. (10) identified high BA as an

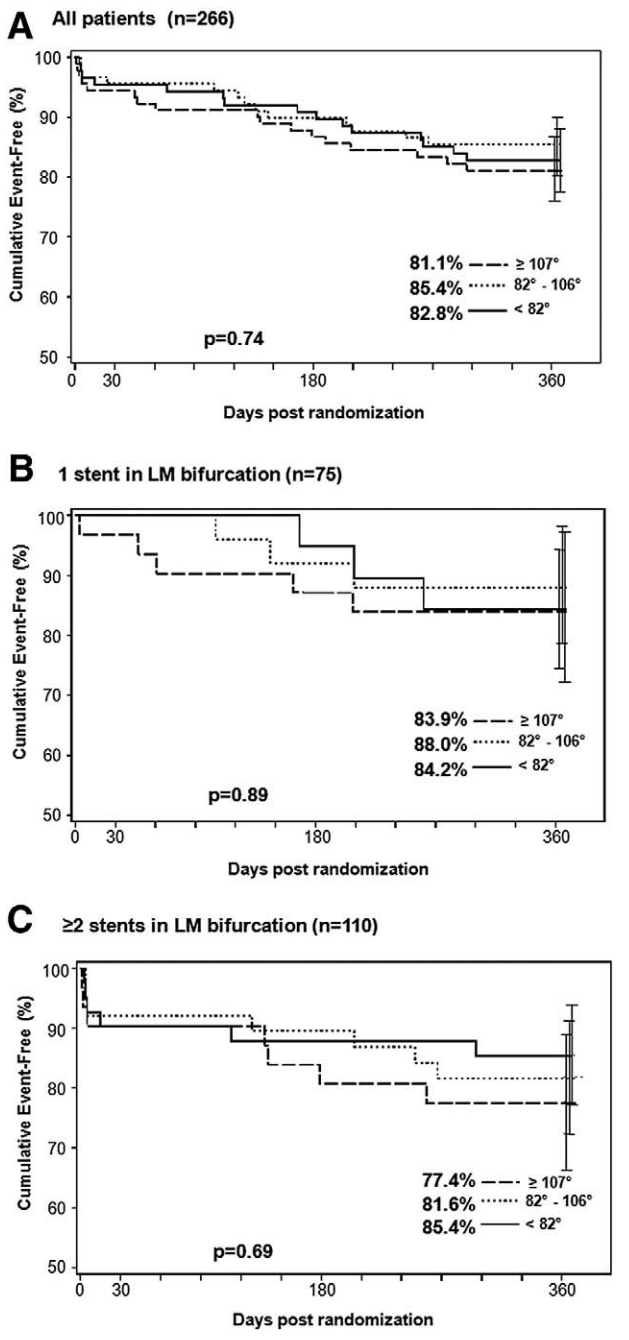

Figure 3. Freedom From MACCE to 12 Months Across Diastolic Pre-PCI Distal BA Values

Kaplan-Meier curves are shown for the entire analyzable cohort (n = 266) **(A)**, the subgroup of patients with 1 stent in the left main (LM) bifurcation (n = 75) **(B)**, and the subgroup of patients with ≥2 stents in the LM bifurcation (n = 110) **(C)**. No significant difference is calculated in any of the panels. Tertile values for diastolic distal bifurcation angle (BA) are reported. The **I bars** indicate 1.5 SE. The p values were calculated with the log-rank test. MACCE = major adverse cardiac and cardiovascular events.

independent predictor of increased major adverse cardiac events at 12 months after crush stenting of bifurcation lesions; this was not the case after main vessel stenting only (11). The study by Chen et al. (12) linked increased TLR rates to higher distal BA values in an LM cohort, whereas an association between high BA values and high restenosis rates has also been verified by Adriaenssens et al. (13) in the context of Culotte stenting, albeit excluding LM cases. However, neither Di Mario et al. (36) nor Kaplan (37) has found in their respective studies evidence that would support this hypothesis; Di Mario et al. (36), like Adriaenssens et al. (13), excluded LM cases from his study.

Ormiston et al. (14) and Murasato (15) have already proven in their bench studies that, in the context of crush stenting, a steep proximal angle and hence a larger distal angle are associated with less optimal expansion and apposition of the SB stent, especially at the site of the ostium.

In contrast, theoretical considerations lead to the conclusion that the outcome of either Crush or Culotte technique would have been adversely influenced by a narrower distal angle; this would be attributable to a more probable carina shift limiting the diameter of the SB ostium in Crush (38) and to an increased stent cell size necessary to span an oblique ostium in Culotte (39). Consequently we are led to speculate that added factors come into play to determine the long-term outcome, such as fluid biomechanics. High and low shear stress areas are supposed to exist in close proximity in steeply angulated bifurcations, thus promoting platelet activation and stasis; Dzavik et al. (10) postulate that an excess of metal in such an area would only aggravate these phenomena, possibly leading to increased rates of thrombosis and restenosis.

Our study did not corroborate the findings of several of the studies referenced. Only when separately studying the cases where ≥2 stents were implanted in the LM bifurcation was there a trend toward lower event rates for the patients with narrower diastolic pre-PCI distal BA values. However, the strength of our study consists in the very fact that the analysts were totally unaware of individual patient data and clinical outcome; thus, this could be considered as a double-blind approach. Moreover, this is the first study correlating 3D QCA-derived angulation data to long-term MACCE; superior assessment of the anatomical changes conferred by PCI will potentially unravel the interplay between geometry and clinical outcome.

Study limitations. This study was performed as an exploratory analysis blinded to individual patient data, treatment, and clinical outcome. Because analysis was independent from the Case Report Form, no relevant subgroup analysis could be performed. Consequently we also could not establish whether the systolic heart motion effect universally outweighs the relevant PCI effect. Moreover, the limited number of events precluded any detailed analysis of MACCE components and increased the probability of a

type II error. A post-hoc calculation revealed a diminished power of either overall or subgroup analysis (not >30% at a significance level of 0.05).

Angulation parameters could not be determined in 25% of patients in the study group; exclusion of one-half of these studies was ascribed to difficult anatomy and inadequate cineangiography, a major confounder being a narrow distal BA. This might have ultimately induced a bias for higher mean distal BA values. However, this was a retrospective post hoc analysis; had the angulation parameters been calculated prospectively and online, a higher rate of complete analysis could have been anticipated.

Conclusions

Three-dimensional BA analysis for the LM, before and after PCI, is feasible; LM angulation parameters vary considerably. Cardiac motion exerts a reciprocal effect on proximal and distal BA, the former being increased and the latter decreased during systole. A PCI modifies the distal BA; overall, angles are decreased, whereas the narrowest pre-PCI angles are actually increased after the procedure. Cumulative event rates throughout the first 12 months after randomization did not differ significantly, when compared across pre-PCI distal BA values. The potential long-term predictive value of these parameters and their prospective applicability during PCI merit further inquiry.

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